Remarks/Arguments:

I. Status of the Application and Claims

Claim 15 is amended herein. Support for the amendment is found throughout the application as originally found, including, for example, Paragraph [0046] of published application US 2004/0258626. No new matter has been introduced.

Claims 1-15 remain pending and under examination.

II. Claim Rejections under 35 U.S.C. § 103

Applicants traverse the rejection of claims 1-15 under 35 U.S.C. 103(a) as being unpatentable over Keller et al. (US 6,645,466; "the Keller reference") in view of Ward et al. (US 6,616,914; "the Ward reference"). Reconsideration and withdrawal of the rejection are respectfully requested in view of the claim amendments and arguments set forth herein.

The present invention is concerned with the realization that close control of the particle size of a lactose carrier in a dry powder formulation provides a formulation that is easy to handle and that can be readily filled into the reservoir of a multidose dry powder inhaler (MDPI). Control of the lactose particle size also provides compositions that are more accurately metered, and provide more uniform and consistent dispersions when dispensed by MDPI devices (see paragraph [0007] of the application as filed). In particular, the inventors have found that the above advantages can be achieved when the lactose particles have a volume mean diameter (VMD) of between 70 and 120 microns and a diameter of less than 250 microns, and where up to 96 % by weight of the lactose particles are less than 150 microns in diameter and up to 25 % by weight of the lactose particles are less than 5 microns in diameter. It should be noted that the lactose carrier used according to the present invention must meet all of these requirements.

The Keller reference discloses compositions comprising carrier particles having a mean particle diameter of approximately 10 to 500 micrometers and preferably approximately 50 to 200 micrometers (see lines 51 to 53 of column 7 of Keller). The Keller reference incorrectly uses the terms "MMAD" and "mean particle diameter" interchangeably (see, for example, column 6, lines 4-5). However, MMAD is known in the art to refer specifically to "mass median aerodynamic diameter", and in relation to the Keller reference the term "MMAD" shall hereafter be used. The formulations of the Keller reference can also contain from about 0.1 to about 10 % by weight of inhalable carrier particles having an "MMAD" of at most 10 microns, preferably at most 5 microns, for at least 50 % of the particles (see lines 8-16 of column 8 of

the Keller reference). The Examiner is of the opinion that the difference between the Keller reference and the present invention is that the Keller reference does not specifically teach carrier particles having a volume mean diameter of between 70 and 120 microns, and that this deficiency is cured by the Ward reference. However, the combination of the Keller and Ward references does not lead to the present invention. Moreover, the Examiner has erred by failing to address the issue of a reason to combine Keller and Ward.

As stated hereinabove, the Keller reference is concerned with dry powder formulations comprising a pharmaceutically inactive carrier of non-inhalable size and a pharmaceutically active compound of inhalable size. In all the examples of the Keller reference, lactose monohydrate is used as the pharmaceutically inactive carrier. The Keller reference seeks to provide a dry powder inhalation formulation that has improved moisture resistance (see abstract of the Keller reference). In complete contrast, the Ward reference is concerned with the provision of a dry powder formulation in which a pharmaceutical acts as its own carrier. The whole thrust of the Ward reference is that inert carrier particles are not used at all. In fact, the first few lines of the abstract of the Ward reference specifically state:

> "In a powder formulation for use in a dry powder inhaler, a pharmaceutical acts as its own carrier, so that the use of lactose or other excipients are not needed."

The effect of the compositions of the Ward references is that the smaller active particles are inhaled to give rapid effect, and the larger active particles are swallowed to give slower onset or a more sustained effect (see lines 32-42 of column 2 of Ward). The fact that the Ward reference makes no use of lactose carrier particles at all means that the skilled person would not have read this document in combination with the Keller reference. The Examiner's position is that the deficiency cured by the Ward reference is the teaching of specific particle sizes of the lactose carrier which are not disclosed by the Keller reference. However, since the Ward reference does not relate to lactose carrier particles at all, the skilled person would not have looked to the Ward reference to address this deficiency. Inert lactose carrier particles and carrier particles composed of an active substance are very different things, and the skilled person would not understand particle sizes of one to be interchangeable with the other. For this reason alone, the present invention is inventive over the Keller reference in view of the Ward reference.

Even if the disclosures of the Keller and Ward references were to be combined, this would not give rise to a composition that falls within the scope of claim 1. The Examiner states that the Keller reference teaches a composition comprising a mixture of lactose particles having a

large particle size of from 50 to 200 microns and a fine particle size of at most 5 microns. This is in contrast to the present invention because the present invention requires a volume median diameter of between 70 to 120 microns. In fact, the differences between the present invention and the disclosures of the Keller and Ward references go beyond what the Examiner has stated.

The Keller reference teaches a large particle fraction of lactose particles having from 50 to 200 microns. Not only is this range broader than the range required by claim 1, it is actually not even directly comparable. This is because the large particle fraction of Keller is defined according to the particles' mass median aerodynamic diameter ("MMAD"). In contrast, the particles of claim 1 are defined according to their volume mean diameter (VMD). These two methods of particle size measurement are different, and do not allow direct comparison.

Turning now to the Ward reference, the Examiner states that disclosed therein are particle sizes of 50-100 microns (column 2, line 54) and 1-5 microns (column 2, line 59) in diameter. Importantly, these particle sizes do not relate to lactose, they instead relate to particles of an active ingredient. So if one combines the Keller and Ward references, a composition according to claim 1 clearly does not result – because the particle sizes required by claim 1 are those of lactose. For this reason alone, the present invention is inventive over the combination of the Ward and Keller references. The skilled person would have to adapt the teachings of the Ward reference by applying the disclosed particle sizes to inert lactose instead of medicament. This is not taught or suggested in either document, and to make such an adaptation requires hindsight gleaned from knowledge of the present invention.

As a final point, the teachings of the Ward reference are further complicated by the fact that, like the Keller reference, the method of particle size measurement used is different from that of the present invention. Ward defines the larger particles according to the volume median diameter. This is in contrast to the present invention that uses volume mean diameter. So, even if the skilled person were to make the unlikely combination of the Keller and Ward references, and then make the untaught modification of the Ward reference, he would still not necessarily arrive at a composition that fell within the scope of claim 1. This is even before one considers the requirement recited in claim 1 that up to 96 % by weight of the lactose particles are less than 150 microns in diameter.

In summary, an ordinarily skilled person would not have combined the Keller and Ward references. Even if they were to combine these two documents, a composition of the present invention would not result. Claim 1 and all claims dependent from claim 1 are therefore inventive over the cited references.

III. Concluding Remarks

This Amendment is believed to place the application is condition for allowance and early and favorable action thereon is respectfully requested. In the event any issues remain, the Examiner is invited to contact Applicants' legal representatives at the telephone number shown below.

Respectfully submitted,

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